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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,809	10/17/2003	Bernd Nickel	ZIPH-009-102	8786

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ANDERSON, JAMES D	

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1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,809	NICKEL ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,18-21 and 23-30* is/are pending in the application.

4a) Of the above claim(s) ___ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,18-21,24,25,27,28 and 30* is/are rejected.

7)☒ Claim(s) *23,26 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 14, 18-21, and 23-30 are presented for Examination

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2007 has been entered.

Terminal Disclaimers

Receipt is acknowledged of the Terminal Disclaimers over USP Nos. 6,693,119 and 6,232,327.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 11/13/2007. The Examiner has considered the cited co-pending U.S. Non-Provisional Patent Applications.

Priority

The present application is a continuation of U.S. Non-Provisional Application No. 09/492,531, filed 1/27/2000 (now USP No. 6,693,119) and a Continuation-in-Part of U.S. Non-Provisional Application No. 09/285,058, filed 4/2/1999 (now USP No. 6,232,327). The present

application also claims priority to German Application Nos. 19946301.8, filed 8/28/1999 and 19814828.0, filed 4/2/1998.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Upon review of the prior filed applications, no support is found in U.S. Non-Provisional Application No. 09/285,058 or German Application No. 19814828.0 for the limitations "treating multi-drug resistant tumors" or "inhibiting angiogenesis or metastasis" with the claimed compounds. The specifications of the above applications are directed to treating tumors but no mention is made of treating *multi-drug resistant* tumors or inhibiting angiogenesis or metastasis. As such, the earliest effective U.S. filing date afforded the instant claims is **1/27/2000**, the filing date of U.S. Non-Provisional Application No. 09/492,531.

Claim Rejections - 35 USC § 102

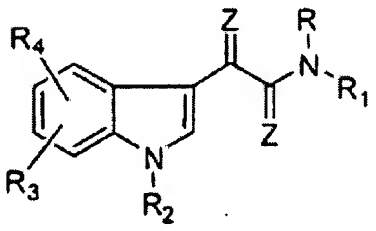
The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 14, 18-21, and 30 are rejected under 35 U.S.C. § 102(e) as being anticipated by **Lebaut *et al.*** (USP No. 6,008,231; Issued Dec. 28, 1999; filed Sep. 8, 1997) (prior art of record) in view of **Dupont *et al.*** (J. Cutan. Med. Surg., 1998, vol. 2, pages 146-152) (newly cited).

The applied reference (LeBaut *et al.*) has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The instant claims recite a method of inhibiting angiogenesis comprising administering a compound of formula I or a physiologically tolerable acid addition salt thereof,



(I)

wherein R is hydrogen, R_1 is optionally substituted pyridine, R_2 is a C_1-C_6 alkyl group monosubstituted with a phenyl group, R_3 and R_4 are selected from the substituents recited in claim 14, and Z is O or S.

Lebaut *et al.* teach novel N-substituted indole-3-glyoxylamides having the same structure as the instantly claimed compounds (col. 1, lines 50 to col. 3, line 39). Specifically, the compounds of Formula I taught in LeBaut *et al.* have the same R-group definitions as the instantly claimed compounds (Table 1). With respect to claim 20, which recites salts of mineral acids or salts of an organic acid, the reference teaches that the compounds of the invention can be present as acid addition salts such as salts of mineral acids or salts of organic acids (col. 3, lines 54-60). With respect to claim 21, which recites specific salts of mineral acids and salts of

organic acids, the same salts as instantly claimed are taught in the reference (*id.*). With respect to claim 30, which recites the specific compound, N-(pryridin-4-yl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxyamide, Lebaut et al. explicitly teach this compound (claim 3). With respect to biological activity, Lebaut *et al.* teach that the compounds of the invention have antiasthmatic, antiallergic, and immuno-suppressant/immunomodulating actions (Abstract) and can be administered to treat diseases such as psoriasis, rheumatoid disorders, and chronic polyarthritis (col. 4, lines 11-15).

Lebaut *et al.* is silent with respect to inhibiting angiogenesis in a patient "in need thereof" as recited in the instant claims. However, administration of the compounds of Lebaut *et al.* to a patient having psoriasis, rheumatoid disorders, or chronic polyarthritis will naturally result in inhibition of angiogenesis, even though this mechanism of action is not recognized by Lebaut *et al.* It is noted that *In re Best.*(195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and

enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Though Lebaut *et al.* does not expressly teach inhibition of angiogenesis (claim 14) as a result of the administration of the disclosed compounds to the subject, the administration of the same compound(s) as claimed (*e.g.*, those identical to Applicant's claimed compounds) to the same host (*i.e.*, subject in need of treatment) as claimed is considered to necessarily have the claimed effect of inhibiting angiogenesis on the subject being treated, whether expressly recognized by Lebaut *et al.* or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

The explanation of an effect obtained when using a compound cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the anti-angiogenesis effect was not itself recognized as a pharmacological effect of administering the disclosed compounds of Lebaut *et al.* for the disclosed therapeutic purpose(s) discussed therein, such an effect is not considered a new therapeutic application because a known therapeutic effect and benefit of using this same active compound(s) was already known in the prior art. Though mechanisms of action of chemical entities are not doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. § 102 is based upon the therapeutic applications and therapeutic effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or combination of chemical compounds, when administered under identical

conditions, is necessarily present, despite the fact that such a property may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

Further, with respect to the limitation "in need thereof" as recited in instant claim 14, Dupont *et al.* (J. Cutan. Med. Surg., 1998, vol. 2, pages 146-152) is provided only as supporting evidence that patients having psoriasis as recited in Lebaut *et al.* are in need of angiogenesis inhibition. In this regard, Dupont *et al.* teach that a number of inflammatory and immune diseases are associated with vascular changes (Abstract). For example, psoriasis is a common inflammatory skin disease with dilation of capillaries as an early histological change (*id.*). In more developed psoriatic lesions there is a proliferation of blood vessels and neovascularization (*id.*). Dupont *et al.* thus prepared extracts of shark cartilage and isolated the active agent, AE-941. This agent was administered to patients having psoriasis to inhibit angiogenesis. The results show that, "Antiangiogenesis agents such as AE-941 provide an entirely new class of agents to treat cutaneous and systemic diseases associated with altered vascularity (Abstract).

Accordingly, the claims are deemed properly rejected as being anticipated by Lebaut *et al.* in view of Dupont *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 14, 18-21, 24-25, 27-28, and 30 are rejected under 35 U.S.C. § 103(a) as being obvious over **Lebaut *et al.*** (USP No. 6,008,231; Issued Dec. 28, 1999; filed Sep. 8, 1997) (prior art of record) in view of **Fiszer-Maliszewska *et al.*** (Zbl. Bakt. Suppl. 13, pages 215-230, 1985) (prior art of record).

The applied reference (Lebaut *et al.*) has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. § 102(e). This rejection under 35 U.S.C. § 103(a) might be overcome by: (1) a showing under 37 CFR § 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a

showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR § 1.131; or (3) an oath or declaration under 37 CFR § 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. § 104, together with a terminal disclaimer in accordance with 37 CFR § 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. § 103(c) as prior art in a rejection under 35 U.S.C. § 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Lebaut *et al.* teach novel N-substituted indole-3-glyoxylamides having the same structure as the instantly claimed compounds (col. 1, lines 50 to col. 3, line 39). Specifically, the compounds of Formula I taught in LeBaut *et al.* have the same R-group definitions as the instantly claimed compounds (Table 1). With respect to claim 20, which recites salts of mineral acids or salts of an organic acid, the reference teaches that the compounds of the invention can be present as acid addition salts such as salts of mineral acids or salts of organic acids (col. 3, lines 54-60). With respect to claim 21, which recites specific salts of mineral acids and salts of organic acids, the same salts as instantly claimed are taught in the reference (*id.*). With respect to claim 30, which recites the specific compound, N-(pryridin-4-yl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxyamide, Lebaut et al. explicitly teach this compound (claim 3). With respect to biological activity, Lebaut *et al.* teach that the compounds of the invention have antiasthmatic, antiallergic, and immuno-suppressant/immunomodulating actions (Abstract) and can be administered to treat diseases such as psoriasis, rheumatoid disorders, and chronic polyarthritis

(col. 4, lines 11-15). Lebaut *et al.* is silent with respect to treating multidrug-resistant tumors, inhibiting angiogenesis, or inhibiting metastasis.

However, Fiszer-Maliszewska *et al.* teach that some neoplasms are very sensitive to immunomodulation, including Ehrlich carcinoma, sarcoma 180, hepatoma L10, and many syngeneic fibrosarcomas (page 215, "Introduction). According to the literature, "immunomodulating agents suppress the growth of several types of neoplasms, including carcinomas" (page 220, first full paragraph). For example, there are studies showing that Lewis lung carcinoma is inhibited by BCG, levamisole, and pyran (*id.*). The growth of Madison lung carcinoma can be retarded by immunomodulators (*id.*). Using these tumor systems, it has been shown that immunomodulation can "control the metastatic spread of tumor cells" (*id.*). With respect to the claimed combination therapy as recited in instant claims 24-27, Fiszer-Maliszewska *et al.* teach that immunomodulation in combination with other modes of tumor therapy has yielded positive results much more frequently (paragraph bridging pages 220 and 221).

In view of Fiszer-Maliszewska, it would have been obvious to one of ordinary skill in the art to use the immunomodulatory compounds of Labaut *et al.* to inhibit the growth and metastasis of tumors. As Fiszer-Maliszewska *et al.* teach that immunomodulation can control the metastatic spread of tumor cells, the skilled artisan would have been imbued with at least a reasonable expectation that administration of the immunomodulatory compounds of Labaut *et al.* would have this therapeutic effect. With respect to claim 25, which recites combination therapy with taxol, doxorubicin, vincristine, or epothilone B, as these agents have been known in the art for years as antitumor agents and in the absence of a showing of unexpected results, it would

have been obvious to use any well known anti-tumor agent in the combination therapy suggested by Fiszer-Maliszewska *et al.* With respect to the pharmaceutical vehicles and administration methods recited in claims 27 and 28, Labaut *et al.* teach formulation of the disclosed compounds in pharmaceutically utilizable excipients and administration forms such as those recited in claim 28.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 10/309,204

Claims 14, 18-21, 24-25, 27-28, and 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-14 and 16-23 of copending Application No. 10/309,204. Although the conflicting claims are not identical,

they are not patentably distinct from each other because the instant claims read on the claims of the '204 application when the compounds are used to treat the cancers recited in '204. For example, one skilled in the art would recognize that treating a prostate carcinoma (recited in the claims of '204) will naturally result in the treatment of metastasis and angiogenesis as instantly claimed. Further, the "comprising" language of the '204 application allows for the administration of other compounds, including the instantly claimed antitumor agents.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

Claims 23, 26, and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

January 25, 2008

1/27/08
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER